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Splenic Involvement by Blastic Mantle Cell Lymphoma (Large Cell/Anaplastic Variant) Mimicking Splenic Marginal Zone Lymphoma

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The most cases of splenic marginal zone lymphoma (SMZL) seem to respond favorably to splenectomy. The diagnosis of this lymphoma is mainly based on the recognition of a micronodular pattern of splenic involvement with marginal zone differentiation. However, it is possible to find so-called "marginal zone differentiation" in splenic involvement by other small B-cell lymphomas, particularly mantle cell lymphoma (MCL) and follicular lymphoma. We report a case of blastic MCL, large cell/anaplastic variant with a high level of clinical aggressiveness, showing biphasic cytology and a micronodular pattern which resembles SMZL. A single biopsy corresponding to this case shows two phases of tumoral progression in a MCL, a rare finding in MCL. In conclusion, the differential diagnosis of SMZL must take the possibility of a blastic MCL with biphasic cytology into account, as the case here. Am. J. Hematol. 62:242–246, 1999. © 1999 Wiley-Liss, Inc.

Key words: spleen; mantle cell lymphoma; marginal zone

INTRODUCTION

The accurate diagnosis of splenic marginal zone lymphoma (SMZL), an entity described only recently, is necessary if the patients in question are to be treated correctly, as they seem to respond favorably to splenectomy [1,2]. The diagnosis of this entity is mainly based on the recognition of a micronodular pattern of splenic involvement with marginal zone differentiation [3–7]. Splenic marginal zone lymphoma shows a biphasic cytology with a central zone of small lymphocytes surrounded by a peripheral zone of larger marginal zone cells containing a variable number of nucleated blastic cells. However, there are several indications which suggest that it is possible to find so-called "marginal zone differentiation" in splenic involvement by other small B-cell lymphomas, particularly MCL and follicular lymphoma [8–10]. We have recently had the opportunity to examine a splenectomy specimen of a case of blastic MCL, large cell/anaplastic variant, which showed conspicuous rings of large cells arranged peripherally with respect to the follicles, in a pattern reminiscent of that found in SMZL. In spite of their architectural location these large cells showed no other morphological features corresponding to marginal zone differentiation.

This case shows the morphology of aggressive transformation in MCL, illustrating the clinical and prognostic significance of differential diagnosis between large-cell MCL and SMZL.

CASE REPORT

A 56-year-old man presented with hemolytic anemia, weight loss, discomfort, huge splenomegaly, and bone marrow and peripheral blood infiltration by low-grade B-cell lymphoma, without peripheral lymphadenopathy. Splenectomy was carried out for the purposes of diagno-

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sis and treatment, at which time hilar and abdominal lymph node together with a liver biopsy were obtained. The patient was treated with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) and radiotherapy, and underwent partial remission. After 2 months the patient was treated for tumoral progression with etoposide, methylprednisolone, cytarabine, and cisplatin (ESHAP). In spite of this treatment, the patient died of tumoral progression 9 months after diagnosis, with widespread disease.

MATERIAL AND METHODS

Sections of spleen, lymph nodes, bone marrow, omentun, and liver were fixed in formalin, embedded in paraffin wax, and routinely stained with haematoxylin and eosin and Giemsa.

Immunostaining was performed on paraffin embedded sections, using the TechMate 500 (DAKO) automatic immunostaining machine. A step of heat-induced epitope retrieval in 0.01 M sodium citrate was included for each antibody prior to immunostaining. The panel of antibodies included CD20, CD3, CD43, CD23, IgM, IgD, κ, λ, CD5 (DAKO), anti-bcl2 (kindly provided by DY Mason), anti-cyclin D1 (DCS6, Novocastra), Mib1 (Immunotech), anti-p53 (DO7, Novocastra), and p21/WAF1 (EA10, Oncogene Science).

RESULTS

Morphology

The spleen weighed 1435 g, and the cut surface had multiple small grey-white nodules that measured 0.1–0.4 cm (a micronodular miliary-like pattern). Sections of spleen showed a nodular infiltrate involving the white pulp (Fig. 1), with scattered smaller nodules present in the red pulp. The nodules consisted of a central area of a homogeneous population of medium sized cells; some of them embedded in an eosinophilic stroma, with monomorphous cytology characterized by irregularly shaped nuclei with sparse cytoplasm. It was possible to see a broad rim of larger cells with irregular large nuclei and finely granular chromatin peripherally disposed around this core of smaller cells, with inconspicuous nucleoli and a higher mitotic index (Fig. 1). There were scattered histiocytes with granular large cytoplasm in both components, although they were more prominent in the blastic one. The concentric disposition of the large cells simulated a marginal zone pattern. No residual germinal centers were observed.

The hilar splenic lymph nodes were enlarged, and measured up to 2.5 cm in diameter. Microscopically, some areas showed a micronodular pattern with the same cellular composition as the one observed in the spleen, with small mantle cells surrounded by large transformed cells. In other areas a diffuse pattern with starry-sky macrophages was observed.

The preaortic lymph nodes analyzed measured up to 3 cm and showed similar histological findings.

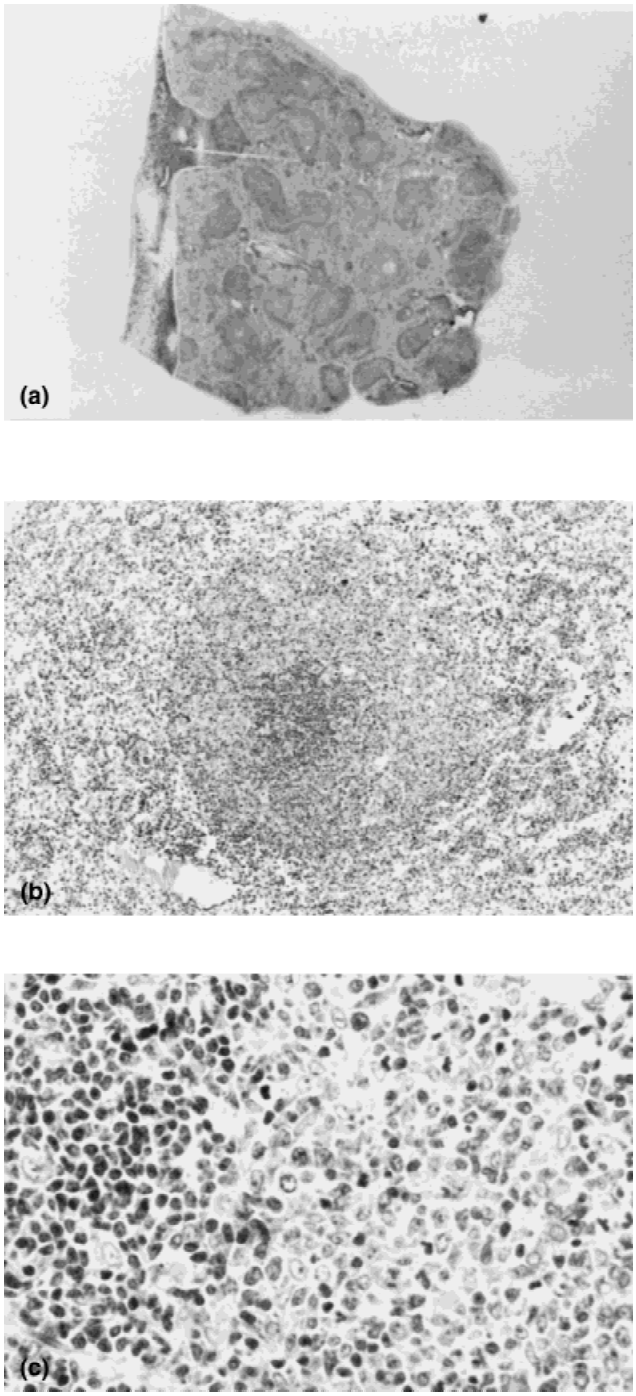


Fig. 1. (a,b) Splenic sections showing a micronodular pattern with peripheral rims of clear cells mimicking a marginal zone pattern. (c) Mantle cells in the left part, surrounded by larger cells with irregular large nuclei. Cytological detail of the blastic component, showing large cells with irregular nuclei, coarse chromatin, and inconspicuous nucleoli.

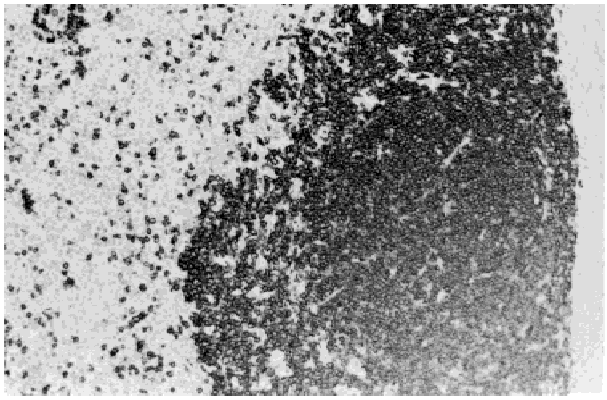
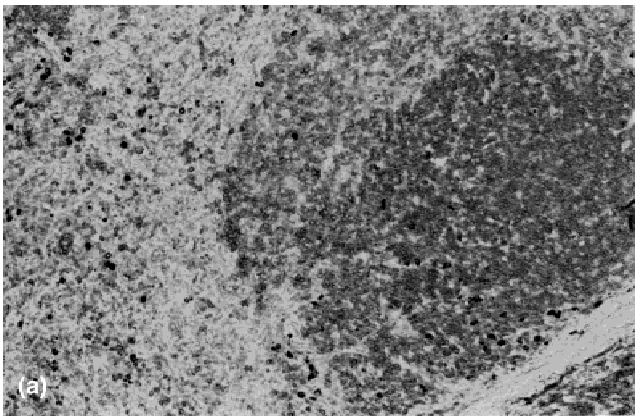


Fig. 2. CD20 immunostaining. Both small and large cells share CD20 reactivity. There is a slight red pulp involvement.



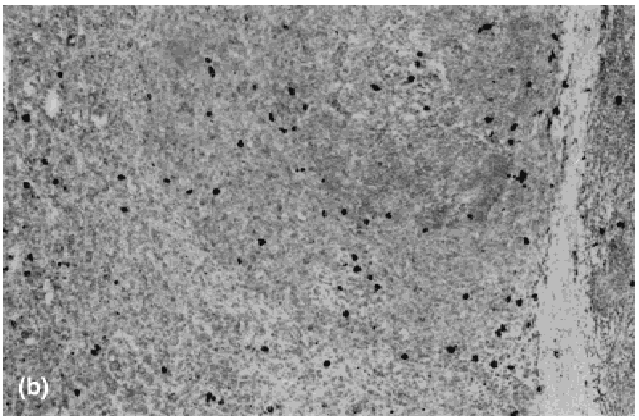
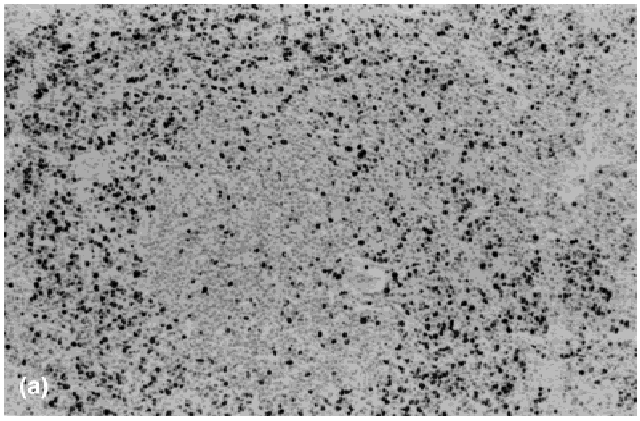


Fig. 3. Both components show the same immunoglobulin light chain restriction pattern: (a) κ; (b) λ.

Bone marrow biopsy showed focal and interstitial infiltration by medium-sized neoplastic cells, with irregular nuclei and large cytoplasm. The liver biopsy and the omentum showed infiltration by classical MC, with a predominance of medium-size cell component.



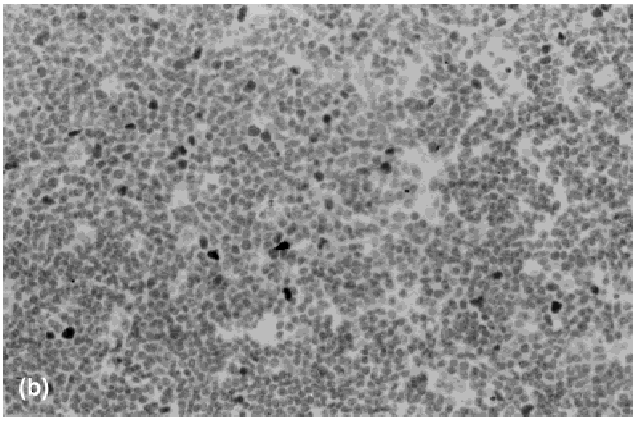


Fig. 4. (a) Proliferation index: high number of MIB1 +ve cells in the periphery, contrasting with the low index within the center of the tumoral nodules. (b) The same situation is found with p53 expression, which is detected mainly in the large cell component.

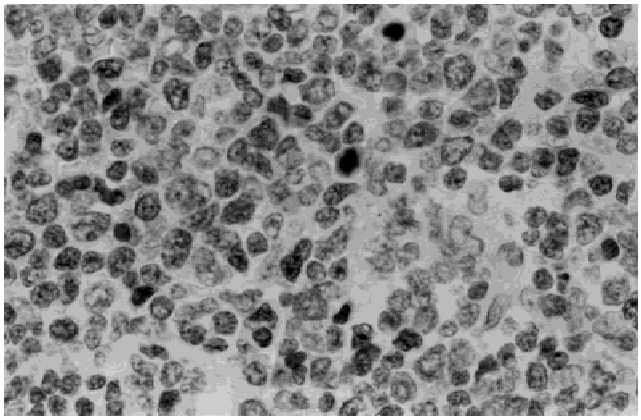


Fig. 5. Cyclin D1 staining showing nuclear CyclinD1 expression by both small and large cell components.

Immunohistochemical Findings

In splenic sections, immunostaining of the neoplastic infiltrate showed expression of CD20, CD43, CD5, IgD, and bcl-2 (Fig. 2). The neoplastic cells were negative for CD3 and CD23. Both component cells showed κ light chain restriction (Fig. 3). Larger cells showed weaker CD43 and CD5 staining.

In the larger cell component a higher number of MIB1 +ve cells (>50%) were distributed in the periphery of nodules, while in the central area the percentage of positive cells was lower (<25%) (Fig. 4). The same cell composition was observed in hilar lymph nodes, with a peripheral disposition of the proliferating large cell component. This peculiar architectural arrangement was not observed in other organs.

The large cell component showed p53 immunostaining in more than 50% of tumor cells, while classical mantle cells situated in the central area only showed scattered positive cells (Fig. 4).

Cyclin D1 overexpression was present in the majority of nuclei in the small and large cell component, although staining was more intense in blastic cells (Fig. 5).

DISCUSSION

Diagnosis of SMZL in the spleen mainly relies on the recognition of a characteristic pattern of splenic involvement, characterized by the presence of perifollicular rims of tumoral clear cells resembling marginal zone B-cells at the edges of micronodules. This diagnosis has relevant clinico-therapeutic implications, since most cases of SMZL seem to behave quite favorably after splenectomy [1,2].

Nevertheless, the case reported here is a tumor that displayed a high level of clinical aggressiveness, although it has an architectural pattern of involvement which resembles that of SMZL but differs from the micronodular and monomorphous pattern usually seen in splenic involvement by classical MCL. There is a striking morphological variation, characterized by the presence of rims of large anaplastic cells arranged in peripheral rings, in an analogous pattern to that usually seen in SMZL. Unlike findings in cases of SMZL, tumoral cells in this case were CD43+, Cyclin D1 positive, and showed a more typical image of monomorphous mantle cells with scattered epithelioid histiocytes (which corresponds to the classical morphology of MCL) inside the core of the tumoral nodules, in the spleen and the hilar lymph nodes.

Aggressive variants of MCL have been shown to exist which harbor either p53 mutation or p16 inactivation [11–15]. Although molecular study of this case failed to show p53 mutation in a PCR-SSCP study (data not shown), the striking p53+, p21/WAF1− immunophenotype found in the large cells of this case reflects the functional inactivation of p53 [16], as different studies have shown beforehand. Thus, p53 mutation or other unknown mechanisms lead to this abnormal accumulation of p53 with a simultaneous absence of p21/WAF1, having been demonstrated that this situation is associated with a shorter survival time in MCL and other NHLs.

This is another and particularly striking example of the pseudomarginal zone pattern (i.e., cells located in the theoretical location of the marginal zone but without the morphology of marginal zone cells) that it is possible to find in many different types of NHL, and now also including the aggressive variant of MCL. It therefore seems that tumoral cells from different lineages may accumulate in perifollicular rims within the spleen, giving a morphological impression that corresponds to tumors in which tumoral cells have the capacity for differentiating into marginal zone cells. There is no evidence in this and similar cases as to why these large transformed cells are found in the theoretical location of the marginal zone, but it is possible that the presence of certain microenvironmental changes may stimulate cell proliferation in this area.

This case illustrates two phases of tumoral progression in a MCL in the same biopsy. Thus although blastic MCL is supposed to arise as a consequence of the accumulation of Cyclin-dependent kinase Inhibitor inactivation on a classical MCL [14], the mixture of both, classic and blastic component, simulating the pattern of a SMZL, has not previously been described, as far as this author is aware. It is probable that the spleen, with its different microenvironments, has the capacity to simultaneously accumulate both components. The differential diagnosis of SMZL must take into account the possibility of a blastic MCL with biphasic cytology, as is the case here.

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